Emerging Therapies for CoVID-19

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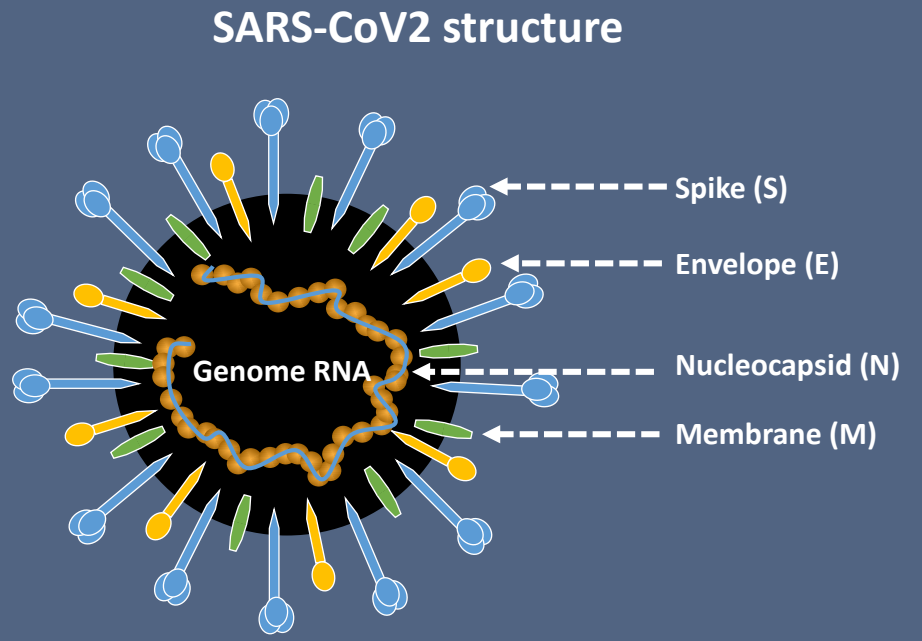
Vice Chair, IHS National Pharmacy & Therapeutics Committee

IHS COVID-19 TeleECHO Session

September 17, 2020

OBJECTIVES

- Identify evidence-based therapies for treatment of CoVID-19
- Review clinical trial characteristics of emerging CoVID-19 therapies
- Examine the availability and staging of leading CoVID-19 vaccines



Adapted from Jin Y et al. Viruses. 2020 March 7

DISCLOSURE STATEMENT

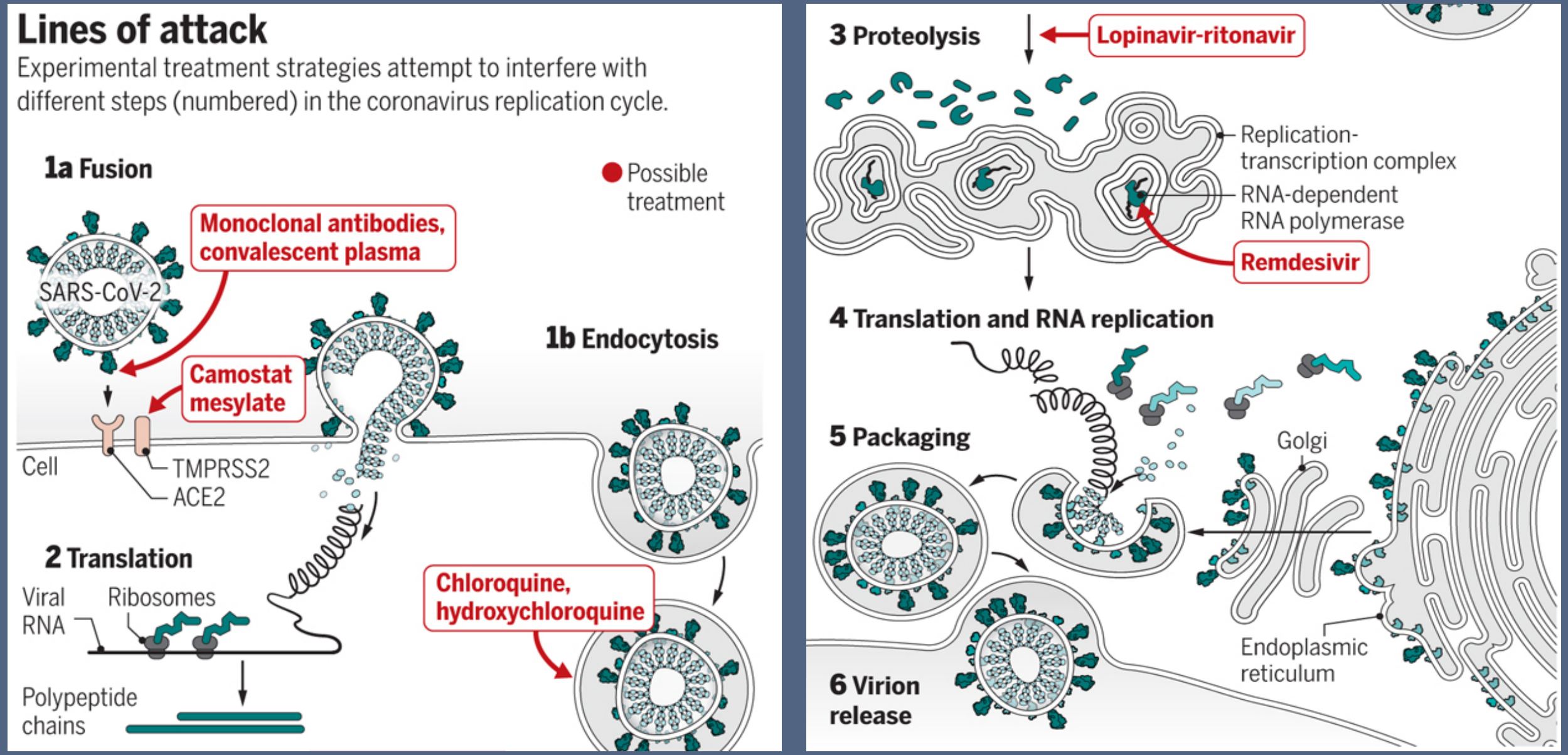
Nothing to disclose

- *I have no financial relationships with commercial entities producing healthcare related products and/or services.*

Potential Therapies: CoVID-19

- >1000 compounds theorized with potential against COVID-19
  - 27 FDA-approved drugs initially identified as candidates (repurposing)
  - Over 20,000 safety-tested (unmarketed) compounds in FDA Database
  - 400,000 natural products available; many using supercomputers to identify computational matches (pharmacophore analysis)
- Over 1200 clinical trials registered globally since March
  - Analysis showed 38% of trials had planned enrollment of <100 patients

1. Krogan, N. How COVID-19 Drug Hunters Spot Virus-Fighting Compounds. Scientific American. March 20, 2020.
2. US Food and Drug Administration. FACT SHEET. www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance
3. Stat-AppliedXL analysis. Data from ClinicalTrials.gov
4. Steele Ji. Medical Press. https://medicalxpress.com/news/2020-06-lab-naturally-compounds-potential-covid-.html. June 19, 2020



Kupferschmidt K, Cohen J (2020) Race to find COVID-19 treatments accelerates. Science (New York, NY) 367:1412–1413

MILKEN INSTITUTE
FasterCures

COVID-19 TREATMENT AND VACCINE TRACKER

LAST UPDATED: **SEPTEMBER 9, 2020 7:06 PM** PACIFIC

FasterCures, a center of the Milken Institute, is currently tracking the development of treatments and vaccines for COVID-19 (coronavirus). This tracker contains an aggregation of publicly-available information from validated sources.

Explore detailed information on each development:

TREATMENTS	VACCINES
317	211
TOTAL	TOTAL

TREATMENT(S)

Category	Number	Examples
Antibodies	80	Recovered antibodies, nanobody antibodies (from llamas), hyperimmune globulins, IL-6 Antags, Endothelial growth factor inhibitors
Antivirals	31	Antiviral drug combinations, protease inhibitors, neuraminidase inhibitors, remdesivir
Cell-Based Therapies	35	Bone marrow stem cells, adipose tissue stem cells, T cells, embryonic cells
Devices	10	Vagus nerve stimulator, blood purification filters, hemolung assist system
RNA-Based Treatments	6	Antisense oligonucleotides; inhaled mRNA, rintatolimod
Scanning Compounds to Repurpose	23	
Other	132	pH barrier, nanoparticles, glucose decoy prodrug, kinase inhibitors, phytodrugs, HCQ, dexamethasone

COVID-19 TREATMENT AND VACCINE TRACKER, FasterCures, a center of the Milken Institute, is currently tracking the development of treatments and vaccines for COVID-19 Accessed on September 10, 2020. Available at: covid-19tracker.milkeninstitute.org/treatment

Assessment of Evidence for COVID-19-Related Treatments: Updated 9/3/2020

The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility's approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use.

ASHP's patient medication information is available at http://www.safemedication.com/. Visit our website for the latest information on current drug shortages.

Selected entries were updated 9/3/20; these can be identified by the date that appears in the Drug(s) column. Within updated entries, select revisions that include the most important new information (e.g., new clinical trial data, new or revised guidance) are marked by **.

TABLE OF CONTENTS

ANTIVIRAL AGENTS

- BALOXAVIR
- UPDATED CHLOROQUINE PHOSPHATE
- FAVIPIRAVIR (Avigan®, Avifavir®, Favilavir)
- UPDATED HIV PROTEASE INHIBITORS (e.g., LPV/RTV, Kaletra®)
- UPDATED HYDROXYCHLOROQUINE (Plaquenil®)
- NEURAMINIDASE INHIBITORS (e.g., oseltamivir)
- UPDATED REMDESIVIR (Veklury•)
- UMIFENOVIR (Arbidol®)

SUPPORTING AGENTS

- ANAKINRA (Kineret•)
- ASCORBIC ACID
- UPDATED AZITHROMYCIN
- BARICITINIB (Olumiant®)
- COLCHICINE
- UPDATED CORTICOSTEROIDS (systemic)
- CORTICOSTEROIDS (inhaled)
- INHALED PROSTACYCLINS
- UPDATED INTERFERONS
- NITRIC OXIDE (inhaled)
- RUXOLITINIB (Jakafi®)
- SARILUMAB (Kevzara®)
- SILTUXIMAB (Sylvant®)
- SIROLIMUS (Rapamune®)
- TOCILIZUMAB (Actemra®)
- VITAMIN D
- ZINC

OTHER

- ACE INHIBITORS, ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)
- UPDATED ANTICOAGULANTS
- UPDATED COVID-19 CONVALESCENT PLASMA
- FAMOTIDINE
- HMG-CoA REDUCTASE INHIBITORS (statins)
- UPDATED IMMUNE GLOBULIN
- UPDATED IVERMECTIN
- NEBULIZED DRUGS
- NICLOSAMIDE
- UPDATED NITAZOXANIDE
- NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIAs)
- TISSUE PLASMINOGEN ACTIVATOR (t-PA; alteplase)

American Society of Health Systems Pharmacists. Assessment of Evidence for COVID-19-Related Treatments Accessed September 10, 2020.

Remdesivir for CoVID-19: challenges of underpowered studies

"…the temptation to lower the threshold of convincing evidence must be resisted, because adopting ineffective and potentially unsafe interventions risks only harm without worthwhile benefit, while making it even harder to undertake trials to find truly effective and safe interventions."

-John David Norrie

Edinburgh Clinical Trials Unit, Usher Institute, Edinburgh EH16 4UX, UK

Norrie JD. Remdesivir for COVID-19: challenges of underpowered studies. Lancet. Published online April 29, 2020.

The DRUGS…

- Hydroxychloroquine / Chloroquine
- Remdesivir
- Dexamethasone
- Convalescent Plasma

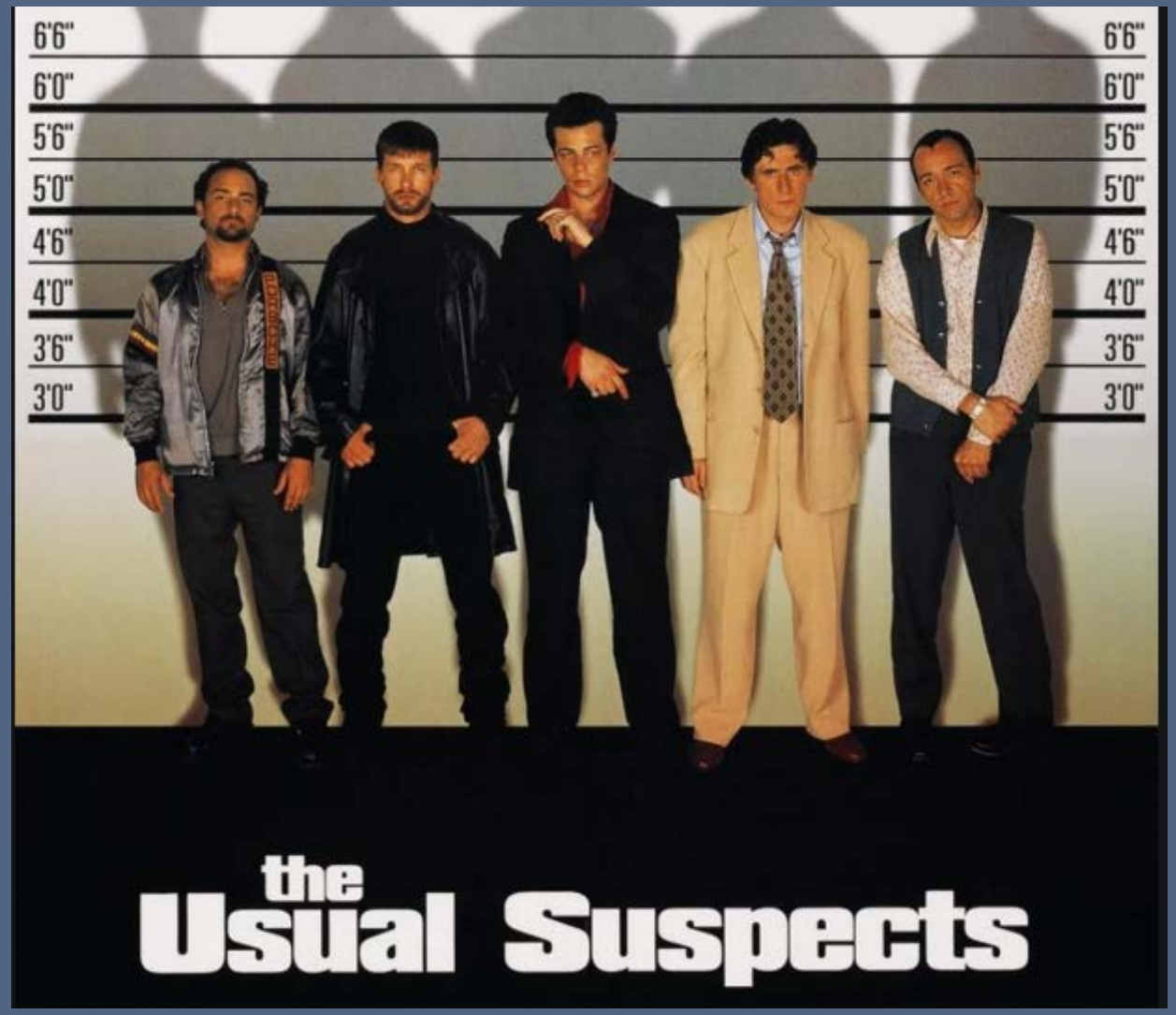


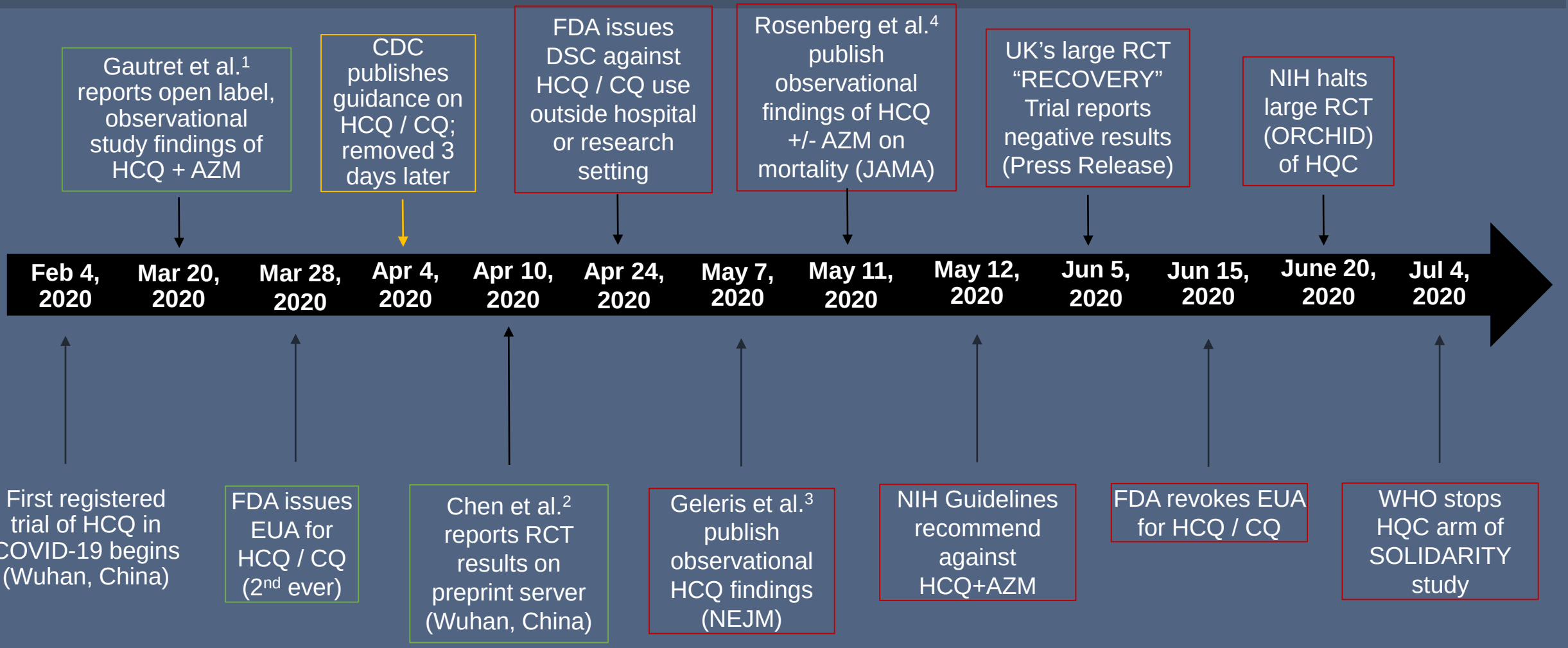
Image courtesy of Imdb.com.

EMERGING THERAPIES: Treatments
-Hydroxychloroquine (HQC)-

- HQC explored in numerous clinical scenarios for treatment AND prophylaxis
  - Mild/moderate/severe disease; Inpatient vs outpatient settings, PEP
- HQC more common than CQ in COVID-19 trials due to:
  - Higher in-vitro activity against SARS-CoV-2; wider availability in the U.S.
- As of July 27th, 2020, 243 trials were registered in ClinicalTrials.gov with HQC included, in various stages of trial progress
  - 24 clinical trial registries that are national, regional, or international in scope
  - July 6 analysis reported *1 of every 6 CoVID studies* included HQC or CQ

Statnews.com. Data show panic and disorganization dominate the study of COVID-19 drugs. Reported July 6, 2020. Available at: https://www.statnews.com/2020/07/06/data-show-panic-and-disorganization-dominate-the-study-of-covid-19-drugs/

CoVID-19 Timeline: Hydroxychloroquine (HQC)



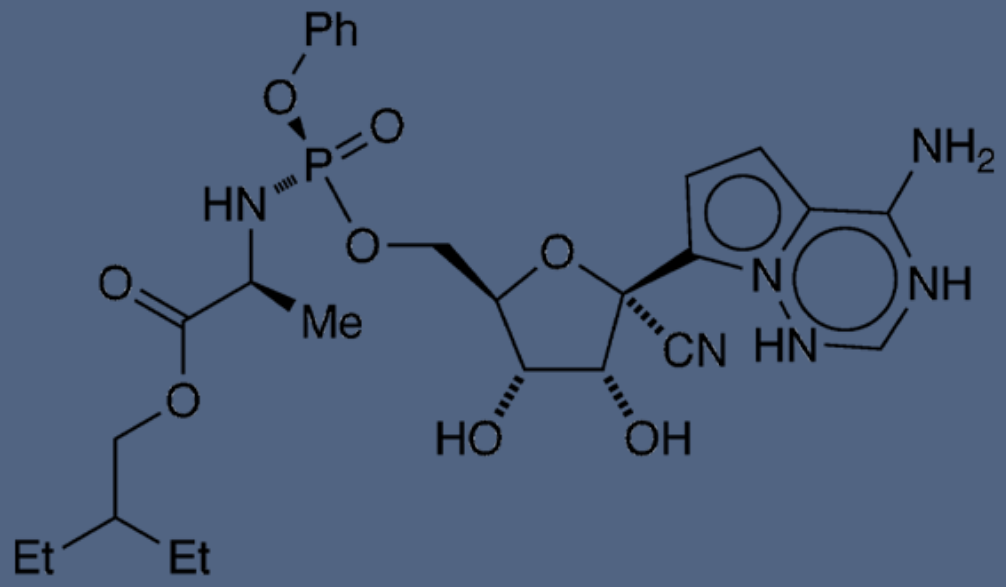
1. Gautret et al. Int J Antimicrob Agents. 20 March 2020. (Epub ahead of print)
2. Chen Z, et al. MedRxiv. Preprint posted online 10 April 2020
3. Geleris et al. N Engl J Med 2020; 382:2411-2418
4. Rosenberg ES, et al. *JAMA*. 2020;323(24):2493-2502

EMERGING THERAPIES: *Hydroxychloroquine (RCTs only)*

Study	Study Design	Comparators	Primary Efficacy Outcome	Safety Outcomes
Chen et al. (mild CoVID +pneumonia); posted 4/10/20 on medRxiv	Single site, non-blinded RCT, N=62, Wuhan, China	UC vs [UC + HQC 400mg QD x 5 days]	Day 5 review of "Time to Clinical Recovery (TTCR)" **-Fever ↓: 3.2 vs 2.2 days, p<0.0008** **-Cough remission: 3.1 vs 2 days, p<0.002**	-2 HQC pts reported mild AEs; no severe AEs -4 pts progressed to severe illness, all PCB
Tang et al. (mild-moderate CoVID); posted 4/14/20 on medRxiv	Multicenter, open-label, non-blinded RCT, N=150, ITT (China)	UC vs [UC + HCQ 1200mg x 3d, 800mg x 2-3 weeks]	Viral clearance @ 28 days; **no difference** (85% vs 81%)	Any AE: (30% vs 9% - mainly GI/diarrhea); Serious AE: (3% vs 0%)
Horby et al. RECOVERY Trial; posted 7/15/20 on medRxiv	Multicenter, DB, RCT, N=4674 (UK) *INTERIM DATA ONLY*	2:1 ratio: UC (N=3132) vs. HQC+UC (N=1542)	28-day mortality: **no difference** (27 vs 25%; RR 1.09, 95% CI: 0.68-1.23)	No differences in: -SVT (7% vs 6%) -VT or AF (0.9% v 0.7%) -1 case of torsades (HCQ)
Skipper et al. (Outpatients only; but sx CoVID/↑ risk) *Ann Int Med; 7-16-20*	Internet-based, multi-site, DB, RCT; N= 423 (US and Canada)	HQC 800mg x1; 600mg in 6-8 hours; 600mg QD x 4 days vs PCB	Change in symptom severity @ day 14 using 10-point visual analogue scale; **No difference:** -0.27; 95% CI: -0.61 to 0.07	Adverse Events: HCQ (43%) vs PCB (22%); *p*<0.001
Cavalcanti et al. (HCQ+AZM in mild-mod CoVID) *NEJM; 7/23/20*	Multicenter, open-label RCT, mITT, N=504 (Brazil)	1:1:1 ratio: UC vs [UC + HCQ 400mg BID] vs [UC + HCQ 400mg BID **+ AZM** 500mg x 7 days]	Clinical status @ Day 15 (7-level ordinal clinical scale): **no difference** between the 3 groups; **no difference** in mortality	Any AE: UC (23%) HQC/AZM (39%) HCQ (34%); AZM (18%) -↑LFTs/QTc prolonged common in HQC/AZM

Guideline Comparison: HQC/CQ (+/- azithromycin)

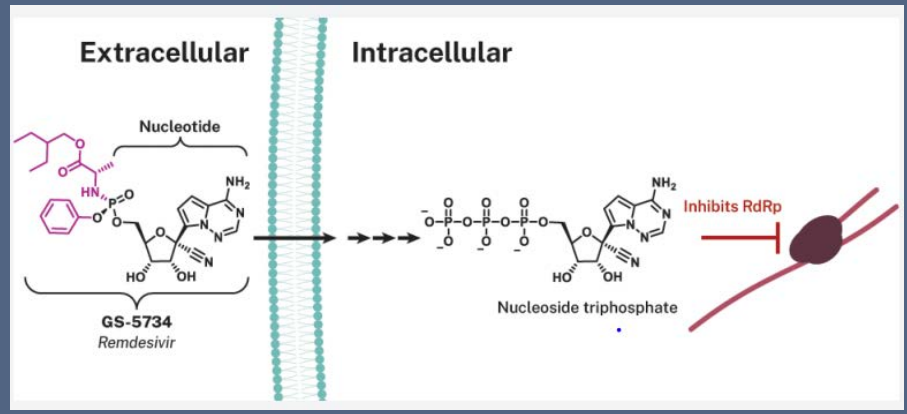
Guideline	Recommendation
IDSA *(Last update: 8/20/20)*	• Among hospitalized patients with COVID-19, the IDSA guideline panel **recommends against hydroxychloroquine**. (Strong recommendation, Moderate certainty of evidence) *Remark: Chloroquine is considered to be class equivalent to hydroxychloroquine.* • Among hospitalized patients with COVID-19, the IDSA guideline panel **recommends against hydroxychloroquine plus azithromycin**. (Strong recommendation, Low certainty of evidence) *Remark: Chloroquine is considered to be class equivalent to hydroxychloroquine*
NIH *(Last update: 8/27/20)*	• The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19 in hospitalized patients **(AI)**. • In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19, except in a clinical trial **(AI)**.



Remdesivir (Veklury®)

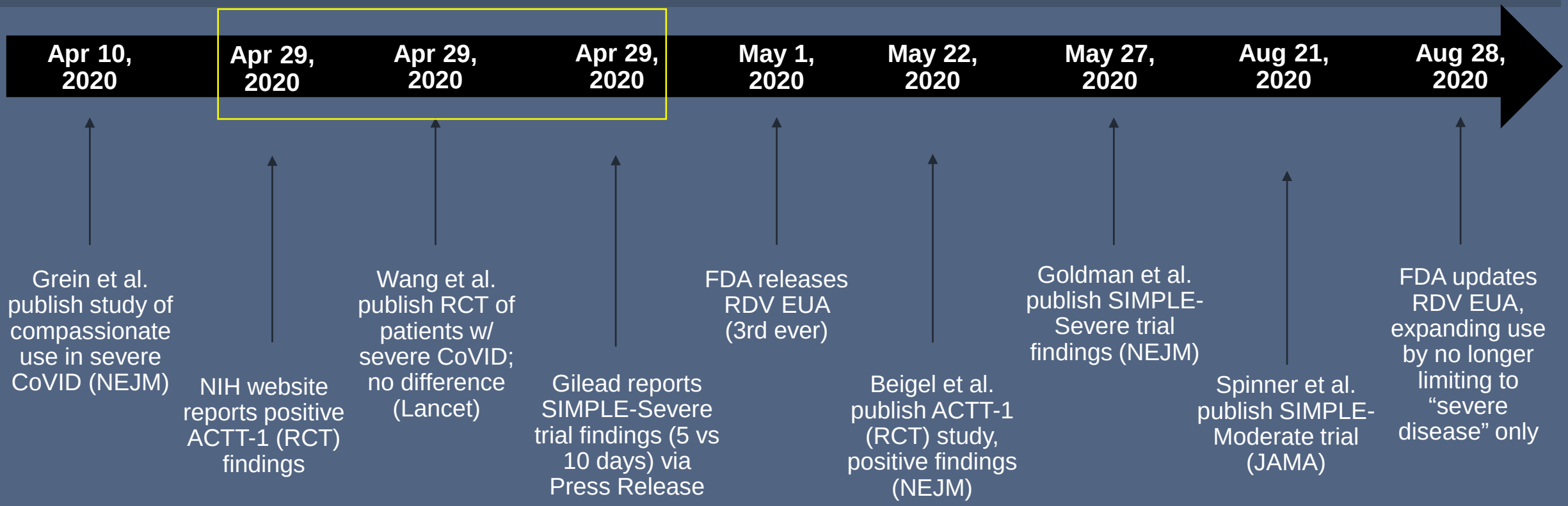
Remdesivir (Veklury®)

- Adenosine nucleotide prodrug that is metabolized intracellularly to form the pharmacologically active substrate remdesivir triphosphate.
- Remdesivir triphosphate inhibits SARS-CoV-2 RNA polymerase which prevents viral replication.
- Originally developed in 2012 as a collaboration between Gilead, CDC and U.S. Army Medical Research Institute of Infectious Diseases
- Tested in 2014 for Ebola virus and found to have activity against coronavirus, MERS



Eastman RT, et al. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. ACS Cent Sci. 2020 May 27; 6(5): 672-683.

CoVID-19 Timeline: *Remdesivir (Veklury®)*



1. Grein J, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med 2020;382:2327-36.
2. Wang Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395: 1569–78.
3. FDA issuance of emergency use authorization for potential COVID-19 treatment. Press release of the Food and Drug Administration, May 1, 2020
4. Beigel JH, et al. Remdesivir for the treatment of Covid-19 — preliminary report. N Engl J Med. 2020 May 22. DOI: 10.1056/NEJMoa2007764
5. Goldman JD, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020 May 27. DOI: 10.1056/NEJMoa2015301
6. Spinner CD, et al. Effect of Remdesivir vs. SOC on clinical status at 11 days in patients with moderate COVID-19. JAMA. 2020 August 21. DOI:0.1001/jama.2020.16349
7. FDA issuance of emergency use authorization for potential COVID-19 treatment. Press release of the Food and Drug Administration, August 28, 2020.

EMERGING THERAPIES: *Remdesivir (RCTs to date)*

Study	Study Design	Comparators	Efficacy Outcomes	Safety Outcomes
Wang et al. (Severe COVID-19) *-APRIL 29, 2020*	Phase 3, multicenter (10 sites in China), DB, RCT, N=237, ITT ELIG: confirmed SARS-CoV-2 + sx ≤12 days + O_2 sat <94% + confirmed pneumonia; Median Age: 65 years	• 2:1 ratio of RDV vs PCB (158 vs 79) • RDV: 200mg x 1 day; 100mg x 2-10 days • Lopinavir/ritonavir, interferons and corticosteroids permitted	• 1* outcome: time to clinical improvement at day 28 (↓ 2 points on 6-point scale, or DC) • **No difference in time to clinical improvement** (HR: 1.23; CI: 0.87-1.75)	• Adverse Events: 66% in RDV pts and 64% in PCB pts • Pts DC due to AEs: 12% RDV (N=18) vs 5% PCB (N=4)
		***Important**: Trial stopped early due to low recruitment; may have been underpowered to detect differences*		
Beigel et al. ACTT-1 (NIAID) *-MAY 22, 2020*	Phase 3, international, DB, RCT, N=1063, ITT ELIG: confirmed SARS-CoV-2 + sx ≤12 days + O_2 sat <94% + confirmed pneumonia; Median Age: 59 years	• 1:1 ratio of RDV vs PCB • RDV 200mg x 1; 100mg X 2-10 days or DC • Enrolled for 28-day period	• 1* outcome: time to recovery defined as 1st day @ categories 1-3 (on 8-point ordinal scale) • 10 days of **RDV superior to PCB** in ↓ days to recovery (**11 vs 15 days; RR=1.32; 95% CI: 1.1-1.5**) • Death: HR 0.7 (0.47-1.04)	• Serious AEs: 21% vs 27% (RDV-PCB) • Serious Respiratory Failure AEs: 5 v 8% (RDV-PCB) • Grade 3-4 AEs: 29% vs 33% (RDV-PCB)
Spinner et al. SIMPLE-Moderate *-AUG 28, 2020*	Phase 3, international, open-label RCT, N=584, ITT ELIG: confirmed SARS-CoV-2 + moderate pneumonia (infiltrates + O_2 sat >94%); Median Age: 57 years	• 1:1:1 ratio of RDV 5 days vs. RDV 10 days vs. UC • RDV: 200mg x 1 day; 100mg x 2-10 days •	• 1* outcome: clinical status on Day 11 (7 point ordinal scale) • **5 days** of RDV **superior** to UC (OR: 1.65, 95% CI: 1.1-2.5, *p*=.02) • No differences in 10 days RDV vs. UC *(Median length of tx: 6 days)* • Death @ 28 days: No differences in any group (1%, 2%, 2%)	• Adverse Events: Nausea (10% vs 3%), hypokalemia (6% vs 2%), and headache (5% vs 3%) more common in RDV users

Guideline Comparison: *Remdesivir*

Guideline	Recommendation
IDSA *(Last update: 9/15/20)*	In hospitalized patients with **severe* COVID-19,** the panel **suggests remdesivir over no antiviral treatment.** (Conditional recommendation, Moderate certainty of evidence) • **Remark:** For consideration in contingency or crisis capacity settings (i.e., **limited remdesivir supply**): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or extracorporeal mechanical oxygenation (ECMO). **Severe illness is defined as patients with SpO_2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.*
	Among patients with severe COVID-19 **on supplemental oxygen** but not on mechanical ventilation or ECMO, the IDSA panel **suggests treatment with 5 days rather than 10 days of remdesivir.** (Conditional recommendation, low certainty of evidence) • **Remark:** In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.
	In patients with COVID-19 admitted to the hospital **without the need for supplemental oxygen** and oxygen saturation >94% on room air, IDSA **suggests against** the routine use of remdesivir. (Conditional recommendation, Very low certainty of evidence)

Guideline Comparison: *Remdesivir*

Guideline	Recommendation
NIH *(Last update: 7/24/20)*	**Because remdesivir supplies are limited**, the Panel recommends that *remdesivir be prioritized* for use in hospitalized patients with COVID-19 who require supplemental oxygen **but** who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO **(BI)**
	Those on **Supplemental Oxygen** but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO: • The Panel recommends using remdesivir for 5 days or until discharge, whichever comes first. • If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed. **(AI)**
	Patients with COVID-19 Requiring High-Flow Oxygen, Noninvasive Ventilation, Mech Ventilation, or ECMO • Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

Dexamethasone

EMERGING THERAPIES: *Dexamethasone*

- Has both anti-inflammatory and immunosuppressive properties
  - Inhibit 2 phases of inflammation; vasodilation and immune cell migration
- In the early days of the SARS-CoV-2 pandemic, based on experience in both SARS and MERS, WHO recommendations cautioned against the use of systemic corticosteroids due to risk of worsening clinical status, delayed viral clearance, and adverse events
- Given the hyper-inflammatory state in COVID-19, immunomodulatory approaches, including steroids, continue to be evaluated to address both ARDS and systemic inflammation.

World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance 13 March 2020. 2020. www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

EMERGING THERAPIES: *Dexamethasone*

Dexamethasone (RECOVERY)
Posted June 22, 2020 on medRxiv

Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report

Running title: Dexamethasone for COVID-19 – Preliminary Report

RECOVERY Collaborative Group*

*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of collaborators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is provided in the Supplementary Appendix.

Correspondence to: Dr Peter W Horby and Dr Martin J Landray, RECOVERY Central Coordinating Office, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom.

Email: recoverytrial@ndph.ox.ac.uk

Word count:
Abstract – 250 words
Main text – 2820
References – 40
Tables & Figures – 2 + 2

Dexamethasone (RECOVERY)
Published July 17, 2020 in NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

ABSTRACT

BACKGROUND
Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

METHODS
In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.

RESULTS
A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

CONCLUSIONS
In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. (Funded by the Medical Research Council and National Institute for Health Research and others; RECOVERY ClinicalTrials.gov number, NCT04381936; ISRCTN number, 50189673.)

The members of the writing committee (Peter Horby, F.R.C.P., Wei Shen Lim, F.R.C.P., Jonathan R. Emberson, Ph.D., Marion Mafham, M.D., Jennifer L. Bell, M.Sc., Louise Linsell, D.Phil., Natalie Staplin, Ph.D., Christopher Brightling, F.Med. Sci., Andrew Ustianowski, Ph.D., Einas Elmahi, M.Phil., Benjamin Prudon, F.R.C.P., Christopher Green, D.Phil., Timothy Felton, Ph.D., David Chadwick, Ph.D., Kanchan Rege, F.R.C.Path., Christopher Fegan, M.D., Lucy C. Chappell, Ph.D., Saul N. Faust, F.R.C.P.C.H., Thomas Jaki, Ph.D., Katie Jeffery, Ph.D., Alan Montgomery, Ph.D., Kathryn Rowan, Ph.D., Edmund Juszczak, M.Sc., J. Kenneth Baillie, M.D., Ph.D., Richard Haynes, D.M., and Martin J. Landray, Ph.D.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Drs. Horby and Landray at RECOVERY Central Coordinating Office, Richard Doll Bldg., Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom, or at recoverytrial@ndph.ox.ac.uk.

*A complete list of collaborators in the RECOVERY trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Horby, Lim, and Emberson and Drs. Haynes and Landray contributed equally to this article.

This article was published on July 17, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2021436

EMERGING THERAPIES: *Dexamethasone* (Randomized Evaluation of COVid-19 thERapY)

The RECOVERY study:

- Open-label, adaptive platform RCT comparing numerous potential treatments to usual care (placebo) in hospitalized patients with confirmed COVID-19.
- 9355 patients, randomized at 176 hospitals across the United Kingdom.
- Active arm participants given dexamethasone 6mg daily, either orally or IV for 10 days or until discharge.
  - A 2:1 ratio of usual care (N= 4,321) to dexamethasone patients (N=2,104) was used. The study began in March 2020 and was halted on June 8, 2020.
- Mean age: 66.1 years, 36% were female. A history of diabetes was present in 24% of patients, heart disease in 27%, and chronic lung disease in 21%. Fifty-six percent of participants had at least one major comorbidity.
- The primary efficacy outcome was 28-day mortality.

The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with CoVID-19 – Preliminary Report. NEJM. 2020 July 17. DOI: 10.1056/NEJMoa2021436

Dexamethasone (RECOVERY Trial): Results

28-day All-Cause mortality:

- occurred 25.7% of UC patients vs. 22.9% in dexamethasone patients
  - RR: 0.83; 95% CI: 0.75-0.93, $p<0.001$
  - NNT = 36

- At 28 days, patients receiving dexamethasone were more likely to be discharged from the hospital
  - RR: 1.11; 95% CI: 1.04-1.19

The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with CoVID-19 – Preliminary Report. NEJM. 2020 July 17. DOI: 10.1056/NEJMoa2021436

Dexamethasone (RECOVERY Trial): -Results from Subgroup Analysis

	Deaths in Usual Care	Deaths in Dexamethasone	Results / Confidence Interval
In mechanically ventilated patients	283 of 683 (41.4%)	95 of 324 (29.3%)	**RR: 0.64** [95% CI: 0.51-0.81], *p*<0.001
	1 death prevented for every 8 ventilated patients who received dexamethasone		
In "oxygen only" patients	682 of 2604 (26.2%)	298 of 1279 (23.3%)	**RR: 0.82** [95% CI: 0.72-0.94], *p*=0.002
	1 death prevented for every 25 patients who received supplemental oxygen and dexamethasone		
No respiratory support	145 of 1034 (14.0%)	89 of 501 (17.8%)	RR: 1.19 [95% CI: 0.91-1.55], *p*=0.14

The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with CoVID-19 – Preliminary Report. NEJM. 2020 July 17. DOI: 10.1056/NEJMoa2021436

EMERGING THERAPIES: *Dexamethasone*

WHO Rapid Evidence Appraisal for CoVID-19 Therapies (REACT) Working Group *(9/2/20)*

- Published meta-analysis of 7 RCTs evaluating corticosteroid use in critically ill COVID-19 patients (N= 1703, median age: 60 years, 29% female)
- Received either dexamethasone, hydrocortisone or methylprednisolone vs UC or placebo
- Primary Outcome: All-cause Mortality @ 28 days

Outcomes:

- Low risk of bias in 6/7 studies; low heterogeneity between studies (I_2=15%)
- **Mortality: OR 0.66, 95% CI: 0.53-0.82 (*p*<0.001)**

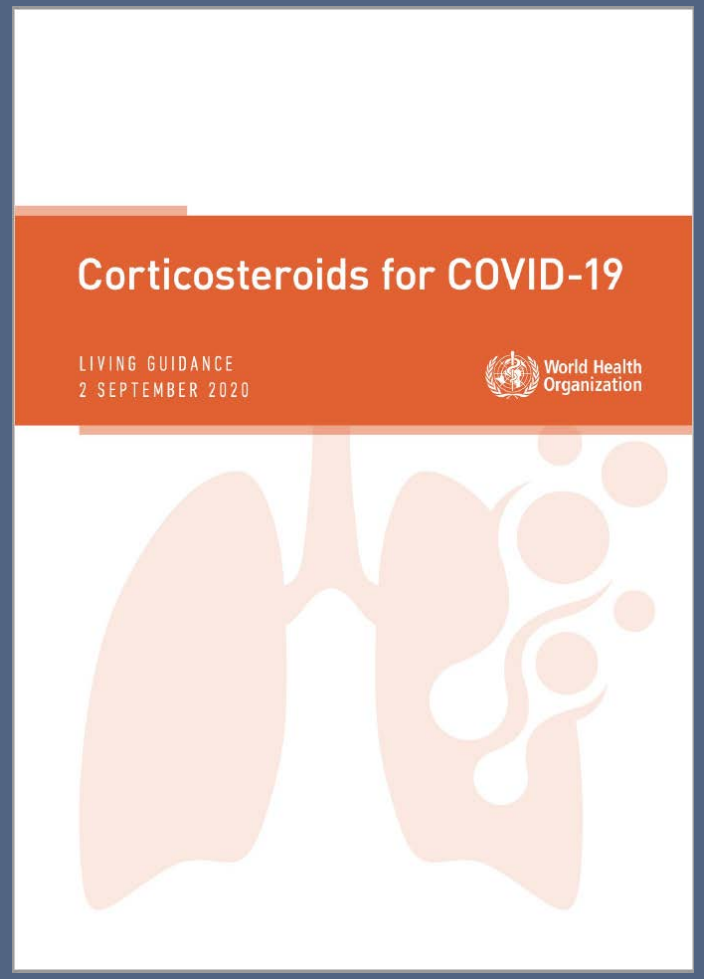
Drug	Odds Ratio	95% CI:	P value
Dexamethasone *(75% of trial patients)*	**0.64**	**0.50-0.82**	**p<0.001***
Hydrocortisone	0.69	0.43-1.12	p=0.13
Methylprednisolone	0.91	0.29-2.87	p=0.87

- More serious Adverse Events reported in those NOT receiving corticosteroids (23% vs. 18%)

WHO REACT Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19. JAMA 2020 Sept 2. DOI: 10.1001/jama2020.17023

EMERGING THERAPIES: *Dexamethasone*

=World Health Organization (WHO) Guidance=



- WHO published "Living Guidance" document on September 2, 2020 to specifically address the role of systemic corticosteroids in COVID-19 treatment
- **Recommendation 1:**
  - We recommend systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with **severe and critical** COVID-19

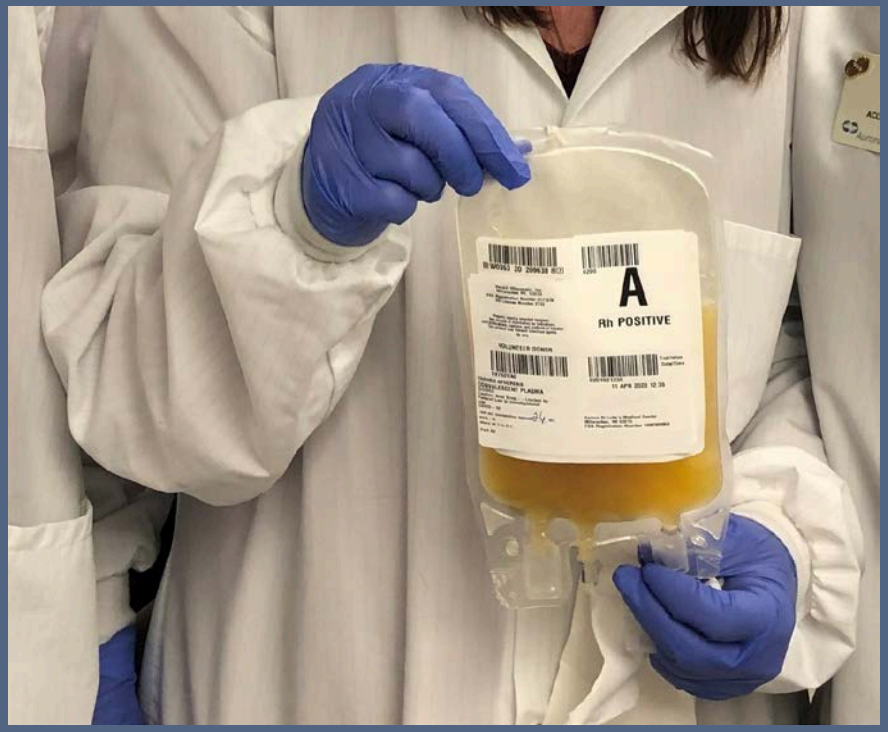
  (strong recommendation, based on moderate certainty evidence).
- **Recommendation 2:**
  - We suggest not to use corticosteroids in the treatment of patients with **non-severe** COVID-19

  (conditional recommendation, based on low certainty evidence).

World Health Organization. Living Guidance: Corticosteroids for COVID-19. 2020 Sept 2. Available at: WHO/2019-nCoV/Corticosteroids/2020.1

Guideline Comparison: Dexamethasone

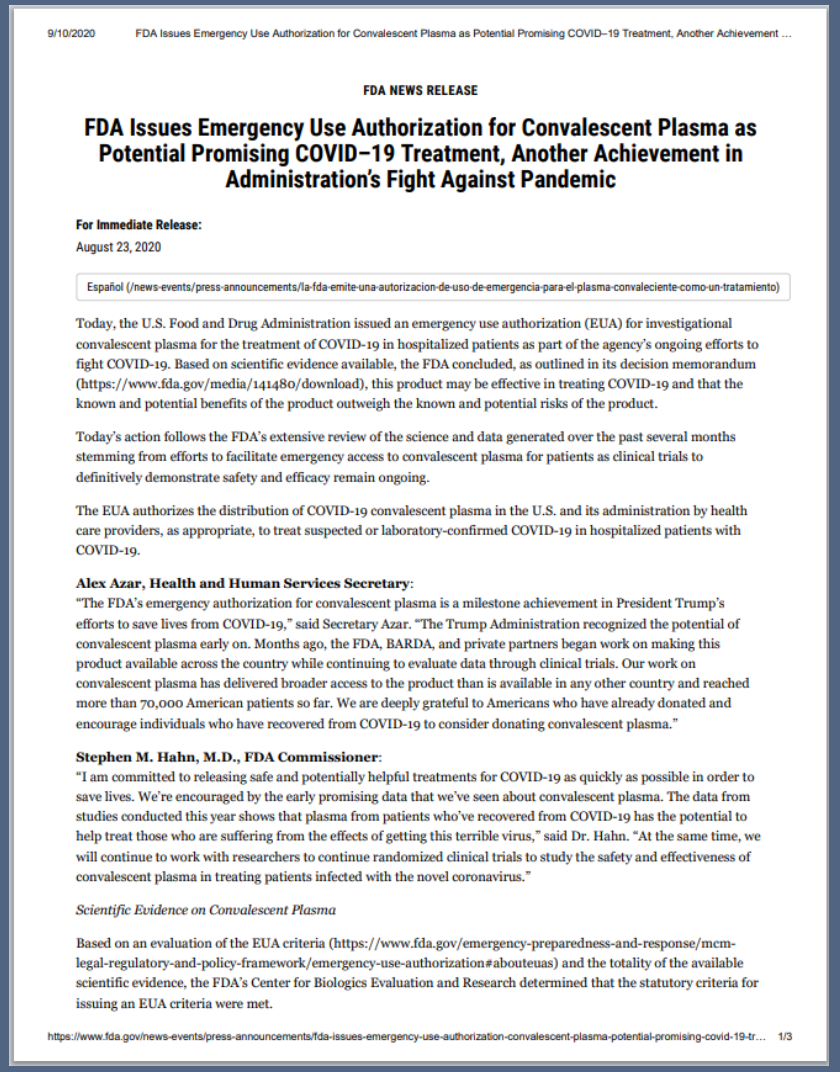
Guideline	Recommendation
IDSA *(Last update: 6/25/20)*	Among hospitalized patients with **severe* COVID-19**, the IDSA panel **suggests glucocorticoids rather than no glucocorticoids.** (Conditional recommendation, Moderate certainty of evidence) • **Remark:** Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg. **Severe illness is defined as patients with SpO_2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.*
	Among hospitalized patients with COVID-19 **without** hypoxemia requiring supplemental **oxygen,** the IDSA panel **suggests against the use of glucocorticoids.** (Conditional recommendation, Low certainty of evidence)
NIH *(Last update: 8/27/20)*	• The Panel recommends using **dexamethasone** 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for COVID-19 treatment in hospitalized patients who are mechanically ventilated **(AI)** and in hospitalized patients who require supplemental O_2 but who are not mechanically ventilated **(BI)**. • The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**. • If **dexamethasone** is not available, the Panel recommends using alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone (AIII)**



www.jsonline.com/story/news/2020/06/18/coronavirus-survivor-plasma-safe-large-study-finds/3212840001/

CoVID-19 Convalescent Plasma

CoVID-19 Convalescent Plasma:
FDA EUA (August 23, 2020)



9/10/2020 FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment, Another Achievement ...

FDA NEWS RELEASE

FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment, Another Achievement in Administration's Fight Against Pandemic

For Immediate Release:
August 23, 2020

Español (/news-events/press-announcements/la-fda-emite-una-autorizacion-de-uso-de-emergencia-para-el-plasma-convaleciente-como-un-tratamiento)

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients as part of the agency's ongoing efforts to fight COVID-19. Based on scientific evidence available, the FDA concluded, as outlined in its decision memorandum (https://www.fda.gov/media/141480/download), this product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.

Today's action follows the FDA's extensive review of the science and data generated over the past several months stemming from efforts to facilitate emergency access to convalescent plasma for patients as clinical trials to definitively demonstrate safety and efficacy remain ongoing.

The EUA authorizes the distribution of COVID-19 convalescent plasma in the U.S. and its administration by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in hospitalized patients with COVID-19.

Alex Azar, Health and Human Services Secretary:
"The FDA's emergency authorization for convalescent plasma is a milestone achievement in President Trump's efforts to save lives from COVID-19," said Secretary Azar. "The Trump Administration recognized the potential of convalescent plasma early on. Months ago, the FDA, BARDA, and private partners began work on making this product available across the country while continuing to evaluate data through clinical trials. Our work on convalescent plasma has delivered broader access to the product than is available in any other country and reached more than 70,000 American patients so far. We are deeply grateful to Americans who have already donated and encourage individuals who have recovered from COVID-19 to consider donating convalescent plasma."

Stephen M. Hahn, M.D., FDA Commissioner:
"I am committed to releasing safe and potentially helpful treatments for COVID-19 as quickly as possible in order to save lives. We're encouraged by the early promising data that we've seen about convalescent plasma. The data from studies conducted this year shows that plasma from patients who've recovered from COVID-19 has the potential to help treat those who are suffering from the effects of getting this terrible virus," said Dr. Hahn. "At the same time, we will continue to work with researchers to continue randomized clinical trials to study the safety and effectiveness of convalescent plasma in treating patients infected with the novel coronavirus."

Scientific Evidence on Convalescent Plasma

Based on an evaluation of the EUA criteria (https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#abouteuas) and the totality of the available scientific evidence, the FDA's Center for Biologics Evaluation and Research determined that the statutory criteria for issuing an EUA criteria were met.

https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-tr... 1/3

"The FDA determined that it is *reasonable* to believe that COVID-19 convalescent plasma *may be effective* in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients."

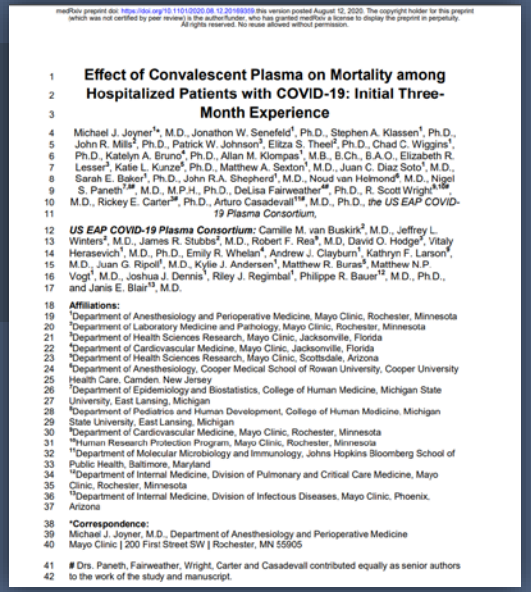
- *"I just want to emphasize this point, because I don't want you to gloss over this number. We dream in drug development of something like a 35% mortality reduction. This is a major advance in the treatment of patients.*

  - Stephen Hahn, MD
  FDA Commissioner

FDA News Release. FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment, Another Achievement in Administration's Fight Against Pandemic. August 23, 2020.

EMERGING THERAPIES: Treatments

-CoVID-19 Convalescent Plasma-



Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience

Michael J. Joyner[1*], M.D., Jonathon W. Senefeld[1], Ph.D., Stephen A. Klassen[1], Ph.D., John R. Mills[2], Ph.D., Patrick W. Johnson[3], Elitza S. Theel[2], Ph.D., Chad C. Wiggins[1], Ph.D., Katelyn A. Bruno[4], Ph.D., Allan M. Klompas[1], M.B., B.Ch., B.A.O., Elizabeth R. Lesser[3], Katie L. Kunze[5], Ph.D., Matthew A. Sexton[3], M.D., Juan C. Diaz Soto[3], M.D., Sarah E. Baker[6], Ph.D., John R.A. Shepherd[3], M.D., Noud van Helmond[4], M.D., Nigel S. Paneth[7,8#], M.D., M.P.H., Ph.D., DeLisa Fairweather[4#], Ph.D., R. Scott Wright[9,10#], M.D., Rickey E. Carter[5#], Ph.D., Arturo Casadevall[11#], M.D., Ph.D., *the US EAP COVID-19 Plasma Consortium*,

US EAP COVID-19 Plasma Consortium: Camille M. van Buskirk[2], M.D., Jeffrey L. Winters[4], M.D., James R. Stubbs[2], M.D., Robert F. Rea[9], M.D, David O. Hodge[3], Vitaly Herasevich[1], M.D., Ph.D., Emily R. Whelan[4], Andrew J. Clayburn[1], Kathryn F. Larson[4], M.D., Juan G. Ripoll[3], M.D., Kylie J. Andersen[1], Matthew R. Buras[9], Matthew N.P Vogt[3], M.D., Joshua J. Dennis[1], Riley J. Regimbal[1], Philippe R. Bauer[12], M.D., Ph.D., and Janis E. Blair[13], M.D.

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***Correspondence:**
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Mayo Clinic | 200 First Street SW | Rochester, MN 55905

# Drs. Paneth, Fairweather, Wright, Carter and Casadevall contributed equally as senior authors to the work of the study and manuscript.

- **Design:** Open-label, Expanded Access Program (EAP)
- **Setting:** 2,807 acute care facilities in the US and territories
- **Participants**: Adult participants enrolled and transfused under the purview of the US Convalescent Plasma EAP program between April 4 and July 4, 2020 who were hospitalized with (or at risk of) severe or life threatening acute COVID-19.
- **Main Outcomes and Measures:** Seven and thirty-day mortality.

Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. *medRxiv*. Posted August 12, 2020. **doi:** 10.1101/2020.08.12.20169359

EMERGING THERAPIES: Treatments
-CoVID-19 Convalescent Plasma-

- **Main Outcomes:** Seven and thirty-day mortality
  - **35,322 transfused patients** had heterogeneous demographic and clinical characteristics.
    - Included a high proportion of critically-ill patients:
      - 52.3% in ICU; 27.5% receiving mechanical ventilation at time of transfusion
  - The **seven-day** mortality rate:
    - 8.7% (95% CI: 8.3%-9.2%) in patients transfused within 3 days of diagnosis
    - 11.9% (95% CI: 11.4%-12.2%) in patients transfused 4 or more days after diagnosis ($p<0.001$)
  - Similar findings were observed in **thirty-day** mortality rates
    - 21.6% vs. 26.7%, p<0.0001

Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. *medRxiv*. Posted August 12, 2020. **doi:** 10.1101/2020.08.12.20169359

EMERGING THERAPIES: Treatments
-CoVID-19 Convalescent Plasma-

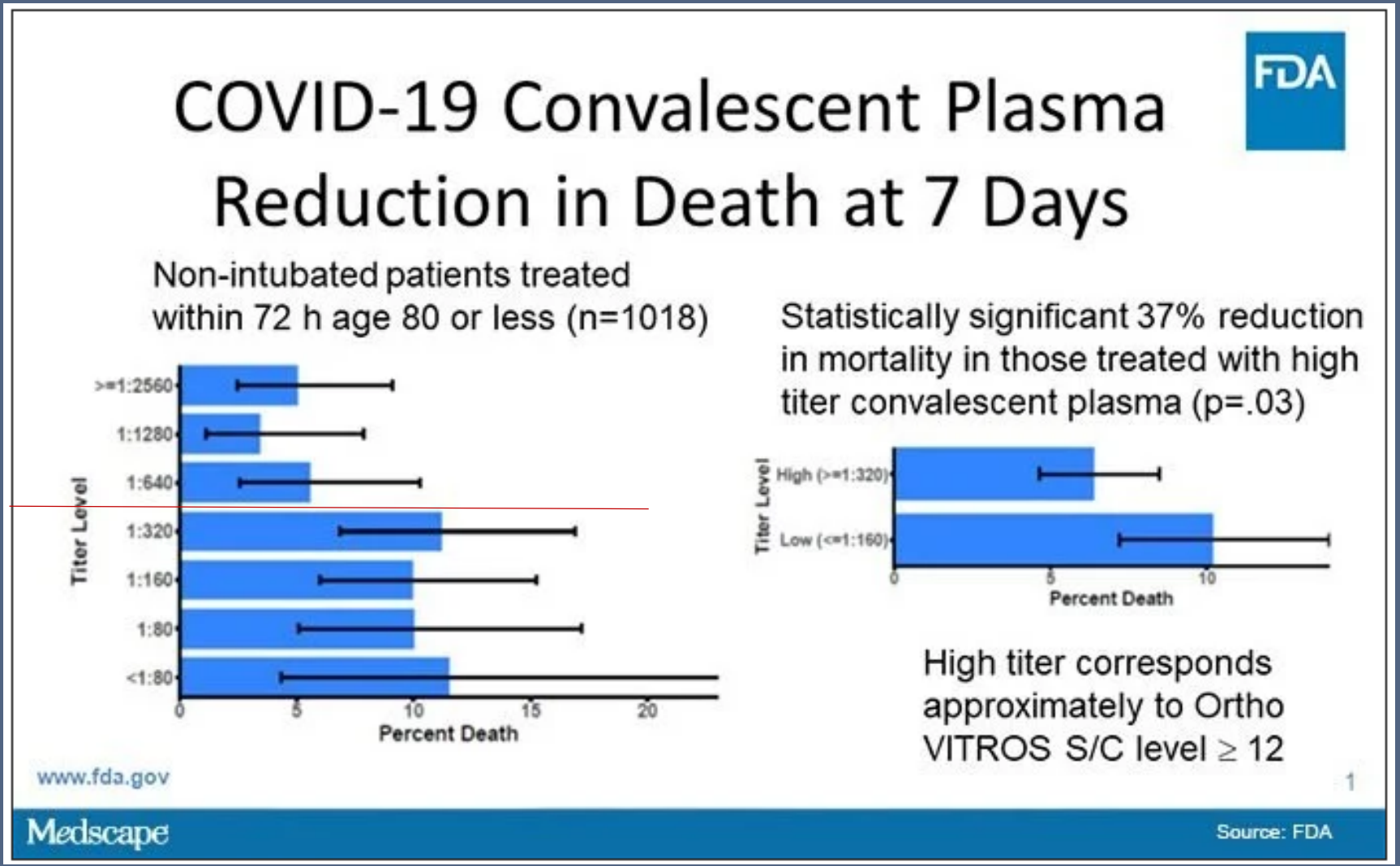
- Importantly, a gradient of mortality was seen in relation to IgG antibody levels in the transfused plasma
  - For recipients of high IgG plasma (>18.45 S/Co), seven-day mortality was 8.9% (6.8%, 11.7%);
  - For recipients of medium IgG plasma (4.62 to 18.45 S/Co) mortality was 11.6% (10.3%, 13.1%)
  - For recipients of low IgG plasma (<4.62 S/Co) mortality was 13.7% (11.1%, 16.8%) (p=0.048)

- The pooled Relative Risk of mortality among patients transfused with high antibody level plasma units was 0.65 [0.47-0.92] for 7 days and 0.77 [0.63-0.94] for 30 days compared to low antibody level plasma units

Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. *medRxiv*. Posted August 12, 2020. **doi:** 10.1101/2020.08.12.20169359

EMERGING THERAPIES: Treatments

-CoVID-19 Convalescent Plasma-



EMERGING THERAPIES: Treatments
-CoVID-19 Convalescent Plasma-

LIMITATIONS:

- Retrospective, observational study of over 35,000 patients who received convalescent plasma, without any controls or untreated patients for comparison.
  - There are no data or evidence from prospective, randomized trials for convalescent plasma to support any survival benefit. The data cited are from a subgroup analysis from a preprint, which is intended to formulate a hypothesis without any definitive findings or conclusions.
- The claim of reduction of mortality was based on improved survival in a subgroup of a subgroup of a subgroup from about 1000 patients, who were partitioned by timing of plasma administration (early vs late), whether they had endotracheal intubation, their age, and level of antibody in the plasma they received.
- The antibody level was determined post facto. This is an illegitimate analysis that, at best, is hypothesis-generating, requiring a prospective, placebo-controlled trial to confirm.
- There are still potential safety issues of convalescent plasma that are unresolved, such as transmission of a virus or immune reaction.

Topol, Eric. Dear Commissioner Hahn: Tell the Truth or Resign. An Open Letter to Stephen Hahn, MD, From Eric Topol, MD. Medscape. Posted August 31, 2020. Accessed on September 1, 2020.

Guideline Comparison: *CoVID-19 Convalescent Plasma*

Guideline	Recommendation
IDSA *(Last update: 9/4/20)*	• Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel **recommends** COVID-19 convalescent plasma **only in the context of a clinical trial**. (Knowledge gap)
NIH *(Last update: 9/1/20)*	• There are **insufficient data** to recommend either for or against the use of convalescent plasma for the treatment of COVID-19. • Convalescent plasma should **not be considered the standard of care** for the treatment of patients with COVID-19. • Prospective, well-controlled, adequately powered **randomized trials are needed** to determine whether convalescent plasma is effective and safe for the treatment of COVID-19. Members of the public and health care providers are encouraged to participate in these prospective clinical trials.

Guideline Comparison:
-Other pharmacotherapeutic agents, classes, etc.

	IDSA	NIH
ACEI/ARBs	NO OFFICIAL RECOMMENDATION: Most professional scientific and medical societies have recommended that ACEI or ARBs be continued in people who have an indication for these medications	Persons prescribed ACEI or ARBs for cardiovascular disease should continue these meds **(AIII)**. The Panel **recommends against** the use of ACE inhibitors or ARBs for the treatment of COVID-19, except in a clinical trial **(AIII)**.
Anticoagulants	**Not addressed**	**Insufficient data to recommend** for or against the use of thrombolytics or increasing doses for VTE prophylaxis in hospitalized COVID-19 patients outside the setting of a clinical trial (BIII). Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis **(AIII)**
Antivirals (Lopinavir/ritonavir)	Recommends the combination of lopinavir/ritonavir **only in the context of a clinical trial**	**Recommends against** using **lopinavir/ ritonavir (AI)** or other **HIV protease inhibitors (AIII)** for the treatment of COVID-19, except in a clinical trial.

Guideline Comparison:
-Other pharmacotherapeutic agents, classes, etc.

	IDSA	NIH
Monoclonal Antibodies (Tocilizumab)	Recommends tocilizumab **only in the context of a clinical trial.**	**Recommends against** the use of anti-IL-6 drugs (e.g., **sarilumab, tocilizumab**) or anti-IL-6 monoclonal antibody (**siltuximab**) for the treatment, except in a clinical trial **(BI)**.
NSAIDs	NO OFFICIAL RECOMMENDATION: Randomized controlled trials are currently underway to better understand the safety of NSAIDs in the management of patients with COVID-19	Persons with COVID-19 taking NSAIDs for a comorbid condition **should continue therapy** as previously directed (AIII). **Recommends that there be no difference** in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 (AIII).
Famotidine	**Suggests against famotidine use** for the sole purpose of treating COVID-19 outside of the context of a clinical trial	**No recommendation(s)**

PREVENTION

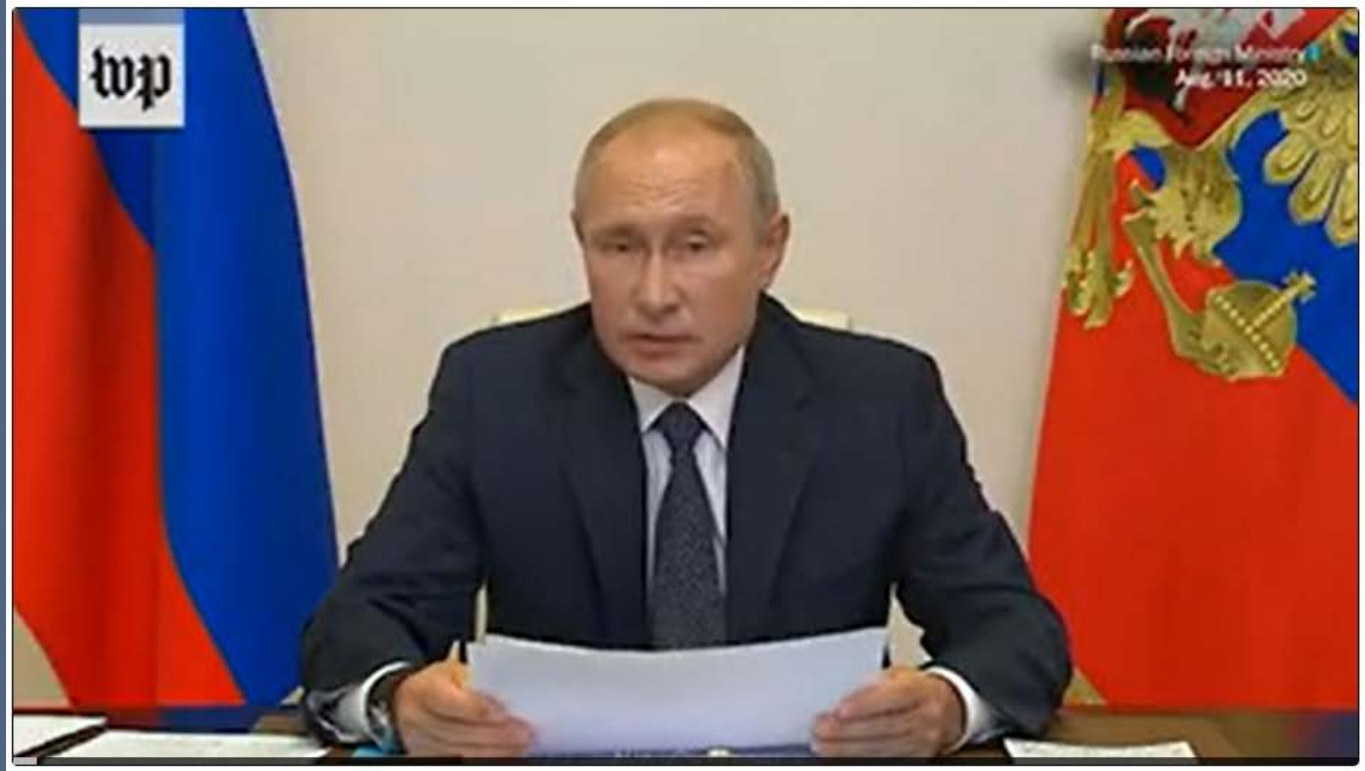

COVID-19
Vaccine
Injection only
5ml store only
COVID-19
Vaccine
Injection only
5ml store only
COVID-19
Vaccine
Injection only
5ml store only

https://www.drugtopics.com/view/us-secures-deal-with-pfizer-biontech-for-100-million-doses-of-covid-19-vaccine-candidate

https://www.drugtopics.com/view/trump-administration-secures-deal-with-moderna-for-100-million-doses-of-covid-19-vaccine

Europe

Russia unveils coronavirus vaccine 'Sputnik V,' claiming breakthrough in global race before final testing complete



Russia claims its "Sputnik V" vaccine works even though it has not undergone Phase 3, the vaccine testing phase used before receiving regulatory approval. (Jhaan Elker/The Washington Post)

"Of course, what counts most is for us to be able to ensure the unconditional safety of the use of this vaccine and its efficiency in the future. I hope that this will be accomplished," Putin said.

By **Isabelle Khurshudyan** and **Carolyn Y. Johnson**

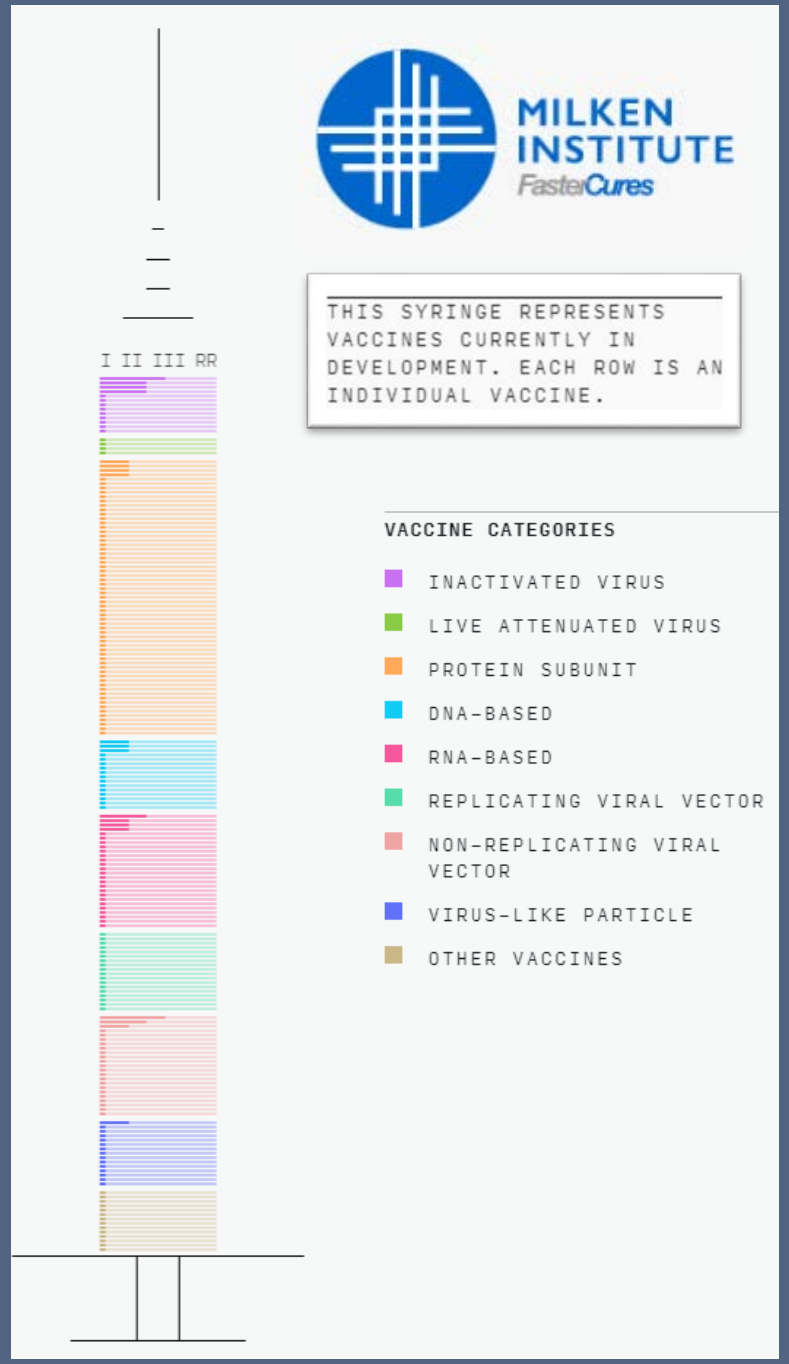
August 11, 2020 at 12:22 p.m. CDT

Sputnik V – formerly known as Gam-COVID-Vac and developed by the Gamaleya Research Institute in Moscow – was approved by the Ministry of Health of the Russian Federation on 11 August. Experts have raised considerable concern about the vaccine's safety and efficacy given it has not yet entered Phase 3 clinical trials.

https://www.washingtonpost.com/world/russia-unveils-coronavirus-vaccine-claiming-victory-in-global-race-before-final-testing-is-complete/2020/08/11/792f8a54-d813-11ea-a788-2ce86ce81129_story.html

EMERGING THERAPIES: =VACCINES=

- 211 vaccines currently in development
  - 31 vaccines are in one of four phases of clinical testing
- 9 different product categories/platforms
- Typical Vaccine Development Timeline = ~10 years
- Possible CoVID-19 Vaccine Timeline = 12-18 months
  - Jan 2020: genetic sequence of SARS-CoV-2 published
  - Operation Warp Speed:
    - Unprecedented public/private collaboration of several US federal government departments including HHS, CDC, FDA, DoD, and the private sector
    - Funding several Phase 3 vaccine trials in return for supply prioritization if successful (300M doses by Jan 1, 2021)

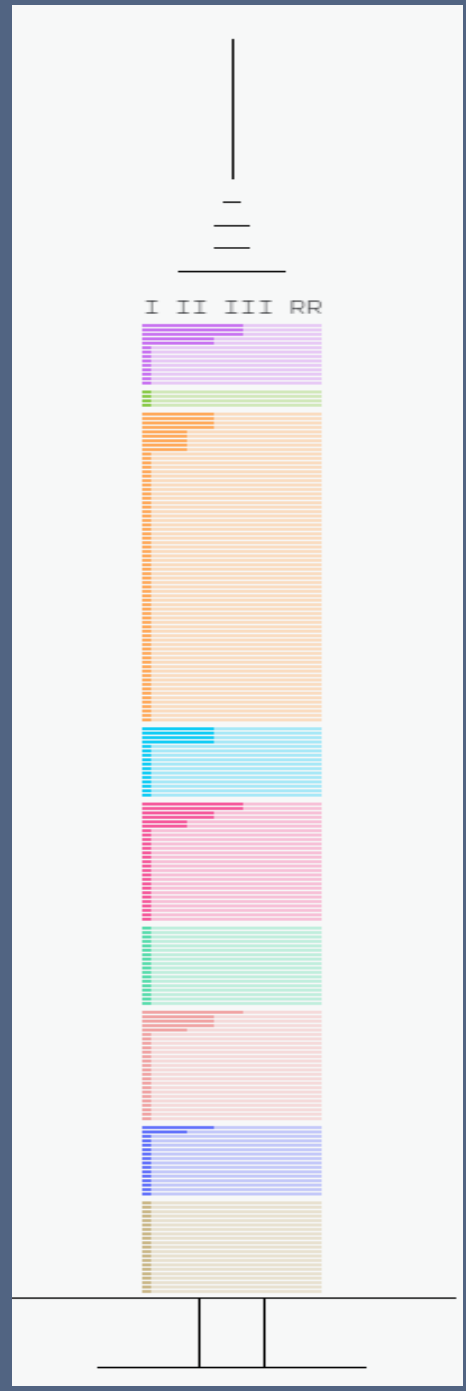


EMERGING THERAPIES: =VACCINES=

Leading Candidates

FARTHEST ALONG*	CLINICAL PHASE	
Univ. of Oxford/AstraZeneca	III	AZD1222*
Sinovac/Instituto Butantan	III	CoronaVac
Wuhan Inst./Sinopharm	III	
Beijing Inst./Sinopharm	III	BBIBP-CorV
Moderna	III	mRNA-1273*
BioNTech/Fosun/Pfizer	II/III	BNT162b2*
CanSino Biologics	II	Ad5-nCoV
Inst. of Medical Biology	II	
Anhui Zhifei Longcom	II	
Novavax	II	NVX-CoV2373*

* Ranked by entry into latest phase of development. Clinical phases move when it is publicly reported that the product has been dosed in a trial.



COVID-19 VACCINE TRACKER: Last updated: **September 10, 2020 8:26 AM PST**

Conclusions / In Summary….

- Presently, hydroxychloroquine/chloroquine have little to no role in CoVID-19 management (treatment or prevention)
- The RECOVERY trial (dexamethasone) and ACTT-1 study (remdesivir) provide the highest caliber, evidence-based guidance to date in the treatment of CoVID-19
- Vaccine development is rapidly evolving; vigilance is required to remain current on vaccine candidates and their availability

Emerging Therapies for CoVID-19

CAPT Ryan Schupbach, PharmD, BCPS, CACP

Vice Chair, IHS National Pharmacy & Therapeutics Committee

IHS COVID-19 TeleECHO Session

September 17, 2020